IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

German, Michael S., et al.

Application No.: 10/733,893

Filed: December 11, 2003

For: DELIVERY OF POLYPEPTIDES BY SECRETORY GLAND EXPRESSION

Customer No.: 20350

Confirmation No. 2608

Examiner: Popa, Ileana

Technology Center/Art Unit: 1633

DECLARATION OF MICHAEL GERMAN UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Michael S. German, hereby declare as follows:

1. I am a co-inventor of the subject matter of U.S. Patent Application 10/733,893, entitled "Delivery of Polypeptides by Secretory Gland Expression" (hereinafter "the '893 application" or "the application").

2. I currently hold the position of Professor in the Department of Medicine at the University of California, San Francisco (UCSF). I am also Clinical Director of the UCSF Diabetes Center as well as Director of the UCSF Hillblom Islet Genesis Network. I received an M.D. from the University of Texas Southwestern Medical School. I have 23 years post-graduate scientific experience, including in fields of cellular and molecular biology. My experience in these areas include methods of transgene expression in cells *in vitro* and *in vivo*. A copy of my curriculum vitae is attached hereto as Exhibit 1.

3. As a co-inventor of the '893 application, and a researcher in the fields of cellular and molecular biology and transgene expression, I am a person of skill in the art to which this invention pertains.

4. I have read the Office Action mailed June 28, 2006 ("Office Action") issued by Examiner Ileana.

5. I understand from the Office Action that the pending claims stand rejected as allegedly obvious over Hickman *et al.*, *Human Gene Therapy*, 5:1477-1483, 1994 ("Hickman") in view of Yang *et al.*, *Proc. Natl. Acad. Sci. USA* 90:4601-4605, 1993 ("Yang").

6. I have read and understand the documents referenced in ¶5 above.

7. The statements set forth herein are offered to address the remarks in the Office Action and to show that Hickman and Yang do not teach that hepatic intraductal administration of naked DNA is an efficient way to deliver proteins to the bloodstream, and further that, as of the filing date of the '893 application, the skilled artisan reading Hickman and Yang would not have led to modify Hickman in the manner proposed by the Examiner.

8. Hickman and Yang discuss two different approaches for liver-directed gene expression, each approach specifically targeting different cell types, as summarized further below.

9. Hickman discusses a method for gene delivery targeting hepatocytes using plasmid DNA. (*See* Hickman at, *e.g.*, p. 1477 (Abstract & Overview Summary) and pp. 1480-1482 (Discussion) .) Specifically, Hickman discusses direct injection of plasmid DNA encoding luciferase, β-galactosidase, or α-1-antitrypsin into liver and further describes the transfection of hepatocytes near the site of injection. (*See id.*, including Abstract and p. 1481, second col. last paragraph, bridging to p. 1481, first col.)

10. In contrast, Yang, which is focused on treatment of cystic fibrosis (CF), discusses the specific, targeted delivery of recombinant adenoviruses to epithelial cells of the biliary tract. (*See* Yang at, *e.g.*, p. 4601 (Abstract) and p. 4602, second col., first full paragraph.) Yang points to the biliary epithelial cells as the primary target for treatment of CF via gene transfer, and specifically teaches away from other strategies that focus "exclusively on the hepatocyte as a target cell." (*Id.* at p. 4602, second col., first full paragraph.) As stated by Yang, the advantage of this approach "is the specificity of gene transfer achieved by virtue of the anatomical constraints of the compartment into which the virus is delivered; the ***primary target***

of gene transfer is the ***biliary epithelial cells***, with recombinant gene expression detected in a ***minority of hepatocytes***." (*Id.* at p. 4604 (emphasis provided).)

11. For at least the reason that Yang discusses a method designed for selective targeting of biliary epithelial cells over hepatocytes, an ordinarily skilled artisan, reading Yang, would not have been specifically and objectively led to use Yang's teachings to modify the method of Hickman, which, in contrast to Yang, is focused on targeting of hepatocytes.

12. I understand that the Examiner states the following with regard to Yang's disclosure:

> Yang et al. clearly teach that hepatocytes can be transfected via intraductal delivery of adenoviral constructs and that the dose of administered adenoviral constructs can be manipulated such that the desired cell type is preferentially transfected. Yang et al. teach that more than 80% hepatocytes can be transfected by using high doses of adenovirus ... and that lowering the dose by 10-fold results in less than 1% transfected hepatocyte, still enough to result in delivery to the bloodstream, according to the teachings of Hickman et al.
>
> [Office Action at p. 5.]

13. The Examiner's statement above does not reflect the totality of Yang's teachings with regard to transfection of hepatocytes. Although Yang shows that some hepatocytes were transfected with recombinant adenovirus, Yang further teaches that the transfection of hepatocytes via the intraductal route is very inefficient, even with the use of adenovirus, a vector normally regarded in the art as providing efficient gene transfer. Yang shows that only the ***maximal*** dose of virus used (2×10^{12} plaque-forming units (pfu)/ml) achieved any significant gene expression in hepatocytes. (*See id.* at p. 4603, first col., first full paragraph (stating that the maximal concentration of virus "demonstrated *lacZ* expression in all of the biliary epithelial cells as well as >80% of the hepatocytes").) Using the next highest dose (1×10^{11} pfu/ml), recombinant gene transfer was observed in only "<1% of all hepatocytes while *lacZ* expression was retained in all intrahepatic bile duct epithelial cells." (*Id.*) This rapid diminishment of gene transfer to hepatocytes, with delivery of submaximal doses of adenoviral vector to the biliary tract, does not reasonably support a conclusion of efficient gene expression into hepatocytes using intraductal delivery.

14. In view of Yang's teachings as discussed above, a skilled artisan reading Yang would not reasonably regard intraductal delivery of a recombinant vector as a particularly suitable means for achieving efficient transfection of hepatocytes. For this reason as well as the reasons previously discussed, the skilled artisan reading Yang and Hickman would not be reasonably be led to substitute Yang's intraductal delivery method for Hickman's method of direct injection into the liver.

15. Even assuming that the skilled artisan were to modify Hickman by substituting Yang's intraductal delivery, per Yang's disclosure, the skilled artisan would use intraductal delivery of recombinant adenovirus rather than naked DNA. Yang's studies pertain only to recombinant gene transfer using recombinant adenovirus. Yang does not discuss the use of naked DNA for transfection of the ductal biliary epithelial cells. Because gene transfer using adenovirus is generally regarded in the art as more efficient than gene transfer with naked DNA, even a teaching of efficient gene transfer to hepatocytes with adenovirus, via an intraductal route, would not reasonably suggest to the skilled artisan that a similar level of gene transfer could be achieved with intraductally delivered naked DNA.

16. Indeed, in view of Yang's relatively poor gene expression in hepatocytes observed with intraductally delivered adenovirus, and because introduction of adenoviral vectors is generally known to be a more efficient means for achieving gene transfer than transfection with naked DNA, the skilled artisan would reasonably view Yang as teaching away from the use of naked DNA for achieving gene expression in hepatocytes by intraductal delivery.

17. For the reasons above, there is no teaching or suggestion in Yang that delivery of a gene to hepatocytes can be achieved using intraductal delivery of naked DNA to the biliary epithelial cells.

18. Therefore, in light of Yang's disclosure and the knowledge in the art as summarized above in ¶¶ 13-17, the skilled artisan reading Yang and Hickman would not be reasonably led to modify Hickman's method of gene transfer to hepatocytes by substituting intraductal delivery of naked DNA for Hickman's direct injection of vector into the liver.

19. Moreover, the skilled artisan would not be reasonably led to modify Hickman with intraductal delivery because Hickman itself teaches away from administration routes other than direct injection into the liver. Only hepatocytes near the site of injection

expressed transgene. Hickman observed that, upon injection into the liver of media with DNA, the media with DNA visibly perfused a wider area of tissue than the limited zone exhibiting expression of the transgene (as shown by X-Gal staining). (*See* Hickman at p. 1480, 1st col., last para. bridging to 2nd col.; and Figure 3.) Hickman concludes from this observation that "hepatocytes were transfected by a physical mechanism related to the actual injection procedure." (*See id.* at p. 1480, 2nd col., top (emphasis provided).)

20. In view of the disclosure discussed above in ¶ 19, the skilled artisan reading Hickman would not look to Yang's procedure of intraductal delivery as an advantageous or even suitable substitute for Hickman's direct injection. Because only hepatocytes near the site of injection were transfected with plasmid, the skilled artisan would not reasonably expect intraductal delivery of naked DNA to hepatic duct epithileum to result in transfection of hepatocytes, located outside of the hepatic duct within the liver parenchyma. While Yang shows some gene transfer to hepatocytes, these results were achieved using recombinant adenovirus at maximal doses, and not with naked DNA. Furthermore, because Hickman attributes gene transfer to hepatocytes to a "physical mechanism" related to the injection procedure, and because Yang's intraductal delivery to biliary epithelial cells would not be reasonably viewed by the skilled artisan as involving physical contact with hepatocytes in the same manner as Hickman's injection, a skilled artisan reading Hickman and Yang would not reasonably expect intraductal delivery of naked DNA to the biliary epithelial cells to achieve gene transfer to hepatocytes.

21. I understand that the Examiner states that Yang *et al.* "clearly teach the advantage of intraductal delivery for gene therapy." I further understand that the "advantage" discussed by Yang to be that delivery can be achieved by a nonsurgical approach, namely endoscopic retrograde cholangiography.

22. Irrespective of any perceived advantage of a "nonsurgical approach," the skilled artisan would not view Hickman as particularly amenable to modification according to Yang's approach, for reasons already discussed above. At the very least, any perceived advantage relating to a non-surgical aspect of intraductal delivery would be considered by the skilled artisan as outweighed by disadvantages as taught by Yang and Hickman, including (a) Yang's teaching of inefficient adenoviral gene transfer to hepatocytes, relative to the biliary epithelial cells, coupled with the knowledge in the art that naked DNA is generally less efficient

than adenovirus for achieving gene transfer; and (b) Hickman's teaching that hepatocytes were transfected by a physical mechanism related to the actual injection procedure, suggesting that administration modes other than direct injection would not necessarily achieve gene transfer to hepatocytes.

23. For at least all of the reasons above, there is no clear and particular motivation in Hickman or Yang to substitute intraductal delivery of naked DNA in Hickman's method.

24. I further declare that all statements made herein of my own knowledge are true and that all statement made on information and belief are believed to be true; and further that I make these statements with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize validity of the application or any patent issuing thereon.

Date: 12/22/06

By: _____

Name: Michael German, M.D.

Title: Professor

EXHIBIT 1

CURRICULUM VITAE

Name: **Michael Scott German**

Position: Professor In Residence, Step 2
Department of Medicine, Diabetes Center, and Hormone Research Institute
School of Medicine
University of California San Francisco

Clinical Director of UCSF Diabetes Center
Member of the Biomedical Sciences (BMS); Pediatric Endocrinology and Diabetes; Diabetes, Endocrinology and Metabolism (DEM); and Molecular Medicine training programs.
Justine K. Schreyer Endowed Chair in Diabetes Research

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EDUCATION:

1975-79	Harvard University, Cambridge, MA	B.A.	*Cum Laude*, Biochemistry
1979-83	Southwestern Medical School, Dallas, TX	M.D.	Medicine
1983-84	University of Arizona, Tucson, AZ	Internship	Internal Medicine
1984-86	University of Arizona, Tucson, AZ	Residency	Internal Medicine
1986-90	University of California, San Francisco, CA	Fellowship	Endocrinology and Metabolism

LICENSES, CERTIFICATION:

1984-1987	Arizona state medical license #15920
1984	Texas state medical license #G7064
1986	California state medical license #A43102
1986	American Board of Internal Medicine certification
1991-2001	Endocrinology board certification

PRINCIPAL POSITIONS HELD:

1990-93	University of California, SF	Adjunct Assistant Professor	Medicine
1993-99	University of California, SF	Assistant Prof. in Residence	Medicine
1999-03	University of California, SF	Associate Prof. in Residence	Medicine
2003-	University of California, SF	Professor in Residence	Medicine

OTHER POSITIONS HELD CONCURRENTLY:

1980-83	University of Dallas	Cross Country and Track Coach
1987-90	UCSF Hormone Research Institute	Fellow
1987-93	San Francisco VAMC	Emergency Room HOD
1990-	UCSF Hormone Research Institute	Principal Investigator
1993-	UCSF Diabetes Center	Member
1993-	UCSF Biomedical Sciences Graduate Program	Faculty
2000-	UCSF Diabetes Center	Associate Director
2001-	UCSF Diabetes Center	Clinical Director
2002-	Program in Developmental and Stem Cell Biology	Member
2003-2005	Program in Human Genetics	Member

TRAINING POSITIONS HELD:

1983-86	University of Arizona Hospitals	Internship and Residency	Internal Medicine
1986-89	University of California, SF	Clinical Fellowship	Endocrinology and Metabolism
1987-90	University of California, SF Hormone Research Institute	Research Fellowship	

HONORS AND AWARDS

1981	NAIA District VIII Women's Cross Country Coach of the Year
1986	Arizona College of Physicians Clinical Vignette Award
1989-1991	National Institutes of Health National Research Service Award
1991-1994	Juvenile Diabetes Foundation Career Development Award
2002	Kenneth R. Crispell Lecture, University of Virginia
2003	Kroc Lecture, University of Alabama
2004	Living and Giving Award, SF Affiliate of Juvenile Diabetes Research Foundation
2005	*Justine K. Schreyer* Endowed Chair in Diabetes Research

KEYWORDS/AREAS OF INTEREST:

German, Michael S.

Diabetes Mellitus, insulin, carbohydrate metabolism, pancreas, islets of Langerhans, beta-cells, developmental biology, stem cell biology, gene expression, transcription factors, microRNA, genomics.

PROFESSIONAL ACTIVITIES

CLINICAL

1990-	Attending Physician UCSF Diabetes Clinic. One half-day clinic per week. I attend on the patients seen by students, residents and fellows.
1993-	Attending Physician Endocrinology Consult Service. Six weeks per year, supervising the clinical fellow, students and residents on the service.
1993-	Instructor, UCSF Diabetes Teaching Center. I lecture once a month at the patient self-management class.
2003-	Clinical Director of the UCSF Diabetes Center.

PROFESSIONAL ORGANIZATIONS

Memberships

Endocrine Society
American Diabetes Association
Juvenile Diabetes Research Foundation
Western Society for Clinical Investigation
American Society for Clinical Investigation

Service to Professional Organizations:

1998	NIDDK Diabetes Research Working Group
2000-	Organizing Committee, Western Regional Islet Study Group
2001-05	Beta Cell Biology Consortium Steering Committee
2004-05	JDRF Research Executive Committee
2004-	ADA SF Leadership Council
2006-	JDRF Islet Research Portfolio Advisory Committee

Service to Professional Publications:

1997-02	Editorial Board, *Diabetes*
1999-	Editorial Board, *Diabetes Technology and Therapeutics*
2002-	Editorial Board, *Journal of Biological Chemistry*

Ad hoc journal reviews include *Proc. Nat. Acad. Sci. USA*, *Nature*, *Development*, *Genes and Development*, *Molecular and Cellular Biology*, *Nature Genetics*, *Journal of Clinical Investigation*, *Journal of Biological Chemistry*, *Diabetes*, *Developmental Dynamics*, *Molecular Endocrinology*.

Service to Professional Meetings:

1993	Co-chair, *Metab III* session, American Fed. for Clinical Research, Western Meeting, Carmel, CA.
1993	Co-chair, *Insulin Secretion* session, ADA Annual Meeting, Las Vegas, NV.
1994	Coordinator and Chair of Scientific Com., Diabetes Symposium in Honor of Gerold M. Grodsky, Ph.D., San Francisco.
1994-01	Chair, Northern California ADA Annual Scientific Meeting.
1996	Chair, Pathways to a Cure, Diabetes Research Symposium, Healdsburg, CA.
1997	Session Chair, Keystone Symposium, Insulin Action and Secretion in NIDDM.
1997	Advisory Board and Moderator, Pancreatic b-Cell and Islet Res 97, Satellite Symp for IDF Congress, Helsingor, Denmark.
1998	Symposium Chair, American Diabetes Association, 58th Annual Meeting, Chicago IL.
1998	Planning Com. and session chair, MODY as Paradigm of the Path of T2 DM, ADA Research Symp., Scottsdale AZ.
1999	Chair, Bay Area Diabetes Retreat, Tiburon, CA.
2000-	Organizing Committee, Western Islet Club.
2001	Chair, Bay Area Diabetes Retreat, Tiburon, CA.
2001-04	Organizing Committee Scientific Sessions Meeting, American Diabetes Association.
2002	Symposium Chair, ADA, 62th Annual Meeting, San Francisco, CA.
2002	Chair, Organizing Committee, Beta Cell Biology Consortium Retreat, Leesburg, VA.
2003	International Advisory Board, International Symposium on Islet Development and Stem Cells in Diabetes, Helsinki, Finland.
2003	Symposium Chair, ADA, 63th Annual Meeting, New Orleans, LA.
2004	Chair, Organizing Committee, ADA, 64th Annual Meeting, Orlando, FL.
2004	Symposium Chair, ADA, 64th Annual Meeting, Orlando, FL.
2004	Chair, UCSF Diabetes Center Retreat, Tiburon, CA.
2005	Chair, UCSF Diabetes Center Retreat, Marconi Center, CA.
2006	Co-organizer, Keystone Symposium, Taos, NM.

INVITED PRESENTATIONS

International

1. International Diabetes Fed. Congress, Washington, D.C., June, 1991: "Transcription Factors in Pancreatic Islet Gene Expression."
2. Symp on Insulin Gene Tx, Hagedorn Research Inst, Denmark, September, 1992: "Glucose Regulation of Insulin Gene Transcription."
3. Internation Diabetes Federation Congress, Kobe, Japan, Novemeber, 1994: "ß-Cell Glucose Sensing and Transcriptional Regulation."
4. Pancreatic Beta-Cell 1994, Satellite Symp for IDF Congress, Kyoto, Japan, Novemeber, 1994: "Regulation of ß-cell gene expression."

5. Human Frontier Sci Prog, Workshop on Lim Proteins, Bischenberg, France, May, 1995: "Beta-Cell Lim-Homeobox Genes".
6. Hagedorn Research Institute, Denmark, May, 1995: "Beta-Cell Gene Expression".
7. JDFI 4th World Conference, Athens, Greece, March, 1997: "Insulin Gene Expression".
8. Osaka University, Osaka, Japan, July, 1998: "Gene Regulation and Differentiation in the Endocrine Pancreas".
9. Osaka University, Osaka, Japan, July, 1998: "Development of the Endocrine Pancreas".
10. Pancreatic b-Cell and Islet Research 98, Girona, Spain, September, 1998: "Transcriptional Mechanisms Underlying Insulin Biosynthesis".
11. Wakayama Forum, Osaka, Japan, Novemeber, 1998: "Insulin Gene Transcription and NIDDM".
12. 5th Internt'l Meeting on T1 DM, Erice, Italy, Decemebr, 1998: "Transcription Factors, b-Cell Development and Insulin Gene Expression".
13. 12th Symp. on Mol. Diabetology, Sendai Japan, Decemeber, 2000: "Genetic Control of Islet Cell Differentiation".
14. Osaka University, Osaka, Japan, December, 2000: "Gene Expression in the Developing Pancreas".
15. Internat'l Symp. on Regulatory Peptides, Boston, MA, September, 2002: "Hierarchy of factors controlling beta-cell differentiation."
16. European Assoc. for the Study of Diabetes, Budapest, Hungary, September, 2002: "Transcription factors and beta-cell differentiation."
17. Keynote Lecture, Int Sym Islet Dev.&Stem Cells in Diabetes, Helsinki, Finland, April, 2003: "Endoderm dif:Key to b-cell replacement".
18. Australian Diabetes Soc., Plenary, Sydney, Australia, August, 2004:"From stem cells to insulin: How close are we to a cure for diabetes?"
19. Australian Diabetes Soc., Symposium, Sydney, Australia, August, 2004: "Genetic control of beta-cell differentiation."
20. International Congress of Endocrinology, Lisbon, Portugal, September, 2004: "Genetic control of the islet differentiation pathway."
21. Molecular Basis of Clinical Diabetes, Sitges, Spain, October, 2004: "Gene Expression Cascades in Pancreatic Development".
22. 16th Symp. on Mol. Diabetology, Ube, Japan, December, 2004: "From stem cells to insulin: New insights into beta-cell genesis."
23. 10th EASD-JDRF Oxford Diabetes Workshop, Oxford, UK, August, 2005: "Insulin Gene Transcription".
24. Avison Biomedical Symposium, Seoul, South Korea, January, 2006: "From stem cells to insulin: genetic control of pancreatic beta-cells".

National

25. American Diabetes Association Annual Meeting, San Antonio, TX, June, 1992: "Metabolic Control of Insulin Gene Expression".
26. American Diabetes Assoc. Annual Meeting, Las Vegas, NV, June, 1993: "Regulation of Gene Expression in the Pancreatic ß-Cell".
27. Keystone Symposium, Molecular Mechanisms Common to Types I and II Diabetes, January, 1994: "ß-Cell Gene Regulation."

28. Endo Society Annual Meeting, Anaheim, CA, June, 1994: "Transcription Factors and ß-Cell Gene Expression."
29. Keystone Symposium, Insulin Action and Secretion, January, 1997: "Role of Homeodomain Factors in Islet Gene Expression."
30. Symposium on 100th Anniversary of Joslin Diabetes Center, Boston, MA, October, 1998: "Regulation of the Insulin Gene".
31. ADA Research Symposium, MODY as Paradigm of the Path of T2 DM, Scottsdale AZ, November, 1998: "Islet Transcription Factors".
32. Endo Society 81st Ann. Meet., San Diego, CA, June, 1999: "Reg. and Dysreg. of Insulin Gene Transcription and Islet Development".
33. American Diabetes Ass., 58th Ann. Meeting, San Diego, June, 1999: "Transcription Factors and Islet Cell Differentiation".
34. Gordon Conference, New Hampshire, July, 1999: "Differentiation in the Endocrine Pancreas".
35. NIH Workshop, Stem Cells, Bethesda, MD, April, 2000: "The Cascade of Gene Expression Events Control b-Cell Differentiation".
36. American Diabetes Ass., 60th Ann. Meeting, Philadelphia, June, 2001: "Transcriptional Regulation of Pancreatic Islet Differentiation."
37. NIH Workshop, Stem Cells, Bethesda, MD, October, 2001: " The hierarchy of factors controlling beta-cell differentiation".
38. NIH Workshop, Beta Cell Biology, Bethesda, MD, November, 2001: "Beta Cell Gene Expression".
39. Endo Society, 84th Annual Meeting, San Francisco, CA, June, 2002: "Molecular Determinants of Beta-Cell Development".
40. City of Hope/Levine Symposium, Anaheim, CA, October, 2002: "Beta Cell Differentiation."
41. Sackler Colloquium, Nat. Acad. Sci., Irvine, CA, October, 2002: "Differentiation of pancreatic beta-cells from progenitor cells."
42. Endo Society, Hot Topics in Endocrinology, New Orleans, LA, November, 2002: "Pathways of beta-cell genesis."
43. Keystone Symposium, Towards Understanding Islet Biology, Keystone, CO, January, 2003: "Molecular control of islet cell genesis".
44. Symposium on Organogenesis, Los Angeles, CA, September, 2003: "Gene expression cascades in pancreatic development".
45. ADA Islet Summit, Chicago, IL, April, 2005: "Transformation of progenitor cells to beta-cells".
46. Digestive Disease Week, Chicago, IL, May, 2005: "Tx factor cascades controlling lineage specification of pancreatic endocrine cells".
47. American Diabetes Association, 64th Ann. Meeting, San Diego, Jun, 2005: "Beta-Cell Gene Expression".
48. City of Hope/Rachmiel Levine Symposium, Universal City, CA, November, 2005: "Gene expression cascades in pancreas development"
49. Keystone Symposium, Pancreatic Islets: From Development to Transplantation, Taos, NM, February, 2006 "Gene Expression Cascades in Islet Development"

Regional and Other Invited Presentations:

50. Phizer Inc., Groton, CT, January, 1992, "Parallel expression of insulin and amylin genes."

51. Endocrinology Grand Rounds, March, 1992: "Metabolic Control of Insulin Synthesis."
52. Endocrine-Metabolism Noon Conference, VA Medical Center, September, 1992: "Metabolic Control of Insulin Gene Expression."
53. Faculty/Staff Seminars, Hormone Research Institute, December, 1993: "Molecular Biology of the ß-Cell."
54. Biomedical Sciences Seminar, December, 1993: "Regulation of Insulin Gene Expression."
55. UCSF Postgraduate Programs, Diabetes Update, March, 1994: "Can We Delay or Prevent Type I Diabetes?"
56. Diabetes Symposium in Honor of Gerold M. Grodsky, Ph.D., April, 1994: "ß-Cell Gene Expression and Diabetes."
57. UCSF Postgraduate Programs, Diabetes Update, March, 1995: "Can We Delay or Prevent Type I Diabetes?"
58. Barbara Davis Diabetes Center, University of Colorado, Denver, March, 1995: "Glucose Sensing and Insulin Synthesis".
59. Vanderbilt University, Nashville, TN, May, 1995: "Regulation of the Human Insulin Gene".
60. Millenium Pharmaceutical, Inc., Cambridge, MA, August, 1995: "Metabolic Regulation of Beta-Cell Genes".
61. Eli Lilly Research Labs, Indianapolis, IN, August, 1995: "Metabolic Regulation of Genes in Pancreatic Beta Cells."
62. Cambridge Health Tech Inst, Gene Quant., February, 1996: "Quantification of Insulin Gene Expression and Implications for Diabetes".
63. UC Berkeley, Dept of Nutritional Sciences, March, 1996: "Metabolic Regulation of Insulin Gene Expression".
64. UCSF Postgraduate Program, Diabetes Update, March, 1996: "Cellular Therapies for Curing IDDM".
65. Chiron Corporation, Emeryville, CA, April, 1996: "Secretory Gland Gene Therapy".
66. UC Riverside, April, 1996: "Molecular Mechanisms for Insulin Gene Transcription".
67. Univ. of Pennsylvania, Philadelphia, PA, November, 1996: "Homeobox Genes and Beta-Cell Differentiation".
68. Reproductive Endocrinology Seminar, February, 1997: " Gene Expression in the Pancreatic Islet."
69. Sequoia Hospital, Redwood City, CA, April, 1997: "Future of Diabetes Treatment: Cell Therapy, Gene Therapy, and Prevention".
70. Metabolex Corporation, Burlingame, CA, August, 1997: "Differentiation in the Pancreatic Islet".
71. University of Texas Southwestern Medical School, Dallas, TX, October, 1997: "Development of the Endocrine Pancreas".
72. University of Texas Southwestern Medical School, Dallas, TX, October, 1997: "Insulin Gene Expression".
73. Genetics Institute, Cambridge, MA, October, 1997: "Development of the Endocrine Pancreas".
74. Endo-Metab Noon Conference, VAMC SF, January, 1998: "Development of the Endocrine Pancreas."
75. UCSF Postgraduate Program, Diabetes Update, March, 1998: "Hypoglycemia: Causation and Prevention".
76. Exelixis Corporation, Redwood City, CA, June, 1998: "Development of the Endocrine Pancreas".
77. Ophthalmology Grand Rounds, October, 1998: "Gene Therapy for Diabetes."
78. Endocrinology Grand Rounds, November, 1998: "Differentiation in the Endocrine Pancreas."

79. Northern Cal ADA Research Symposium, San Francisco, CA, December, 1998: "Development of the Pancreatic Beta-Cell."
80. UCSF Postgraduate Program, Diabetes Update, March, 1999: "What is New in Diabetes Related Research".
81. Mol. and Cell. Research Conference, SFGH, February, 2000: "Development of the Endocrine Pancreas."
82. UCSF Postgraduate Program, Diabetes Update, March, 2000: "What Can Mice Tell Us About Human Diabetes?"
83. UC Irvine, Medicine Grand Rounds, April, 2000: "Diabetes in Mice and Men (and Women)".
84. Joslin Diabetes Center, Boston, MA, April, 2000: " Transcriptional control of insulin gene expression".
85. Baylor College of Medicine, Houston, TX, October, 2000: "Development of the Endocrine Pancreas."
86. Yale U. School of Med., New Haven, CT, November, 2000: "Islet Cell Regeneration."
87. Takeda Pharmaceutical, Osaka, Japan, December, 2000: "Gene Expression in the Developing Pancreas".
88. Amylin Pharmaceuticals, San Diego, CA, January, 2001: "Development of the endocrine pancreas".
89. Biochemistry Faculty Research Conference, February, 2001: "Gene Network Controlling Pancreatic Development."
90. Genteric Corporation, Alameda, CA, March, 2001: "Gene Therapy for Diabetes".
91. Geron Corporation, Redwood City, CA July, 2001: "Birth of the Beta-Cell: Genetic Control of Islet Development".
92. Diabetes Center Conference, July, 2001: "Hierarchy of Signals Controlling Pancreatic Development."
93. Opthalmology Grand Rounds, October, 2001: "Islets, beta-cells and stem cells: Future treatments for diabetes."
94. Metabolism Club, Carmel, CA, February,20 02: "New Beta-Cells for Old".
95. UCSF Postgrad Program, Diabetes Update, March, 2002: "Stem Cells, Islet Transplantation: Emerging Treatments for Type 1 DM".
96. Endocrinology Grand Rounds, March, 2002: "From Stem Cells to Beta-Cells: New Insights into Beta-Cell Genesis".
97. University of Chicago, Chicago, IL, April, 2002: "From Stem Cells to Insulin: New Insights into Beta-Cell Genesis"
98. Northern Cal ADA Research Symposium, San Francisco, CA, April, 2002: "Genes Controlling Beta-Cell Genesis."
99. Ligand Pharmaceuticals, San Diego, CA, June, 2002: "HNF4 and Pancreatic Islet Development."
100. Crispell Lecture, U. of VA, Charlottesville, VA, September, 2002: "From stem cells to insulin: How close are we to a cure for Diabetes?"
101. Carousel of Hope Symposium, Beverly Hills, CA, October, 2002: "Gene expression profiling of beta cell genesis."
102. Beta Cell Biology Consortium Retreat, Washington, DC, November, 2002: "Gene expression in islet progenitor cells."
103. UCSF Postgrad Program, Diabetes Update, March, 2003: "New approaches to insulin therapy".
104. Kroc Lecture, U. of Alababma, Birmingham, AL, April, 2003:"From stem cells to insulin: How close are we to a cure for Diabetes?"

105. Northern Cal ADA Res Symp, San Francisco, CA, April, 2003:"From stem cells to insulin: How close are we to a cure for Diabetes?"
106. UCSF Diabetes Center SAB Meeting, October, 2003: "Filling in the Islet Differentiation Pathway".
107. Larry L. Hillblom Foundation 2nd Annual Scientific Session, San Francoisco, CA, November, 2004: "The UCSF Islet Genesis Network".
108. Oregon Health Sciences University, Portland, OR, November, 2003: "From Stem Cells to Insulin: New Insights into Beta-Cell Genesis"
109. UCSF School of Medicine Career Fair, February, 2004: "Careers in Endocrinology".
110. Larry L. Hillblom Foundation 3rd Annual Scientific Session, Los Angeles, CA, November, 2004: "The UCSF Islet Genesis Network".
111. Molecular Medicine Conference, January, 2005: "From stem cells to insulin: New insights into beta-cell genesis".
112. Endocrinology Grand Rounds, January, 2005: "From stem cells to insulin: New insights into beta-cell genesis".
113. Faculty Research Series, February, 2005: "Gene Networks in Development of the Endocrine Pancreas".
114. UCSF School of Medicine Career Fair, February, 2005: "Careers in Endocrinology".
115. UCSF Postgrad Program, Diabetes Update, March, 2005: "Stem Cell Research: An Update".
116. Federation of International Physicians, Fremont, CA, April, 2005: "Stem cells and diabetes".
117. Swedish/California Stem Cell Symp, San Francisco, CA, April, 2005: "Insulin production from stem cells for the treatment of diabetes".
118. UCSF Diabetes Center Conference, May, 2005: "Islet Development."
119. UCSF Preparing Future Faculty, panel discussion, July, 2005: ""Knowing Your Options: Different Paths to Success in Academia"
120. Symposium in Genomics and Stem Cell Research, San Francisco, CA, September, 2005: "Stem Cell Research Clinical Applications."
121. Larry L. Hillblom Foundation 4rd Annual Scientific Session, Novato, CA, November, 2005: "The UCSF Islet Genesis Network".
122. Astra Zeneca Norway talk September 06
123. San Francisco VA Medical Center Medical Grand Rounds, San Francisco, CA, September, 2006: "From stem cells to insulin: How close are we?"
124. Stowers Institute for Medical Research, Kansas City, Mo, May, 2006: "Gene Expression Cascades in Pancreas Development"
125. Vanderbilt U. Medical School, Endocrine Grand Rounds, Nashville, TN, March, 2006: "Gene Expression Cascades Controlling Development of the Endocrine Pancreas."
126. Boston University Medical School, Evans Medical Research Seminar, Boston, MA, March 2006: "From Stem Cells to Insulin: How to Make a Beta-Cell"

Lay Presentations/Interviews

127. UCSF Diabetes Symposium, October 1996: "A New Insulin: Lispro (Humalog)".
128. JDFI, San Francisco Affiliate, May 1997: "Diabetes Research".
129. ADA California Affiliate's Annual Meeting, June 1997: "Cell Therapy for Diabetes".
130. Diabetes Center Advisory Council, July 1997: "Diabetes Research Update".

131. JDFI, San Francisco Affiliate, January 1998: "Diabetes Research".
132. JDFI, Monterey Affiliate, January 1998: "Diabetes Research".
133. JDFI, San Francisco Affiliate, July 1999: "Cell and Gene Therapy for Diabetes".
134. JDFI, Fresno Affiliate, May 1999: "Diabetes Research".
135. UCSF Diabetes Symposium, May 1999: "Beta-Cell Replacement Strategies".
136. JDFI, Los Angeles Affiliate, March 2000: "Cell and Gene Therapy for Diabetes".
137. ADA National Board Meeting, February, 2002: "Stem Cells and Beta-cell Replacement".
138. Yale Club, San Francisco, CA, April 2003: "Stem cells: Science, medicine and politics".
139. Newspaper interview, *Boston Globe*, August, 2002.
140. Testimony, California State Senate Appropriations Committee, Sacramento, CA, May, 20003.
141. Television interview, "To The Contrary", PBS, April, 2004
142. ADA National Board Meeting, February, 2004: "Stem Cells and Beta-cell Replacement".
143. Magazine interview, *Insulin-Free Times*, March, 2004.
144. On line interview, diabetesstation.com, May, 2004.
145. Magazine interview, *Forefront*, Summer/Fall, 2004.
146. UCSF Foundation Annual Meeting, October, 2004: "Stem Cells and Diabetes".
147. Newspaper interview, *San Francisco Chronicle*, December, 2004.
148. Cal Tennis Club, January, 2005: "Stem cells: Science, medicine and politics".
149. Radio interview, This Week in Science, KDVS 90.3 FM, January, 2005.
150. US Senate Appropriations Committee Staff, February, 2005, presentation, Q&A and tour.
151. Newspaper interview, *San Francisco Examiner*, February, 2005.
152. Magazine interview, *Countdown*, Spring, 2005.
153. Newspaper interview, *Contra Costa Times*, July, 2005.
154. Magazine interview, *Fortune*, August, 2005.
155. Children's Diabetes Foundation of the N Bay, Petaluma, CA, Oct., 2005: "Stem Cells and Diabetes".
156. Magazine interview, *New England Journal of Medicine*, October, 2005.
157. Magazine interview, *Nature*, October, 2005.
158. California Institute for Regenerative Medicine (CIRM) Public Meeting, Spotlight on Diabetes, Palo Alto, CA, February, 2006, "Embryonic stem cell research and diabetes".
159. For Grodsky
160. UCSF Diabetes Patient Symposium, San Francisco CA, May, 2006: "Stem Cell Research Updates"
161. UCSF Mini Med School, San Francisco CA, May, 2006: "From insulin to stem cells: How close are we to a cure for diabetes?"

GOVERNMENT and OTHER PROFESSIONAL SERVICE:

<u>GRANT REVIEWS: Peer Review Committees:</u>

1996-1999 American Diabetes Association Review Com.
1999-2002 Juvenile Diabetes Research Foundation, Medical Science Review Committee, Training Grants

2003-	Juvenile Diabetes Res. Foundation, Med. Sci. Review Committee, Islet Biology and Transplantation
2003-	NIH, SBIR/STTR Special Review Study Section

GRANT REVIEWS: Ad Hoc:

7/96, 6/98, 6/99, 6/01	NIH, Metabolism Study Section
3/01, 10/01	NIH, Endocrinology Study Section
6/96, 6/97	NIH, Diabetes Center Review Committee
8/98, 8/01	NIH, NIDDK Special Emphasis Review Committee
2001-05	NIH BCBC Pilot and Feasibility Grant Review
6/05	NIH, Cellular Aspects of Diabetes and Obesity Study Section
11/05	NIH, ZRG1 F06 (NRSA Fellowship)
1994-2000	Veterans Administration
1996-	British Diabetic Association
1999	National Science Foundation
2000-	Israel Science Foundation
10/03	Juvenile Diabetes Research Foundation, JDRF/French partnership
6/04	Juvenile Diabetes Research Foundation, JDRF/Singapore partnership

UNIVERSITY and PUBLIC SERVICE

UNIVERSITY SERVICE

UCSF Campus-Wide:

1987-2002	UCSF Racing Team member
1994-2000	Juvenile Diabetes Foundation Walk for the Cure, UCSF Captain
2005-	Stem Cell Research Programming Committee

School of Medicine:

1995-2000	Diabetes Center Director Search Committee
2001-	Metabolism Block Strategic Planning Committee (Co-director)
2002-	School of Medicine Admissions Committee

Departmental Service:

1993-2000	Diabetes Center Campaign Committee
1995-	Diabetes Center Council
1998-1999	Department of Medicine/Diabetes Center Junior Faculty Search Committee
1998-1999	Department of Medicine/Diabetes Center Clinical Director Search Committee
2000-	Department of Medicine/Diabetes Center Clinical Faculty Search Committee
2001-	Diabetes Teaching Center Planning Committee
2001-2003	Diabetes Clinic Budget Committee (Chair)
2001-2004	Endocrinology/Metabolism Clinic Renovation Committee (Chair)
2002-2005	Diabetes Center Junior Faculty Search Committee
2002-2003	Department of Medicine/Diabetes Center DM Teaching Center Director Search Committee
2003	Department of Medicine Promotion Committee, Subcommittee member
2004-	Department of Medicine Promotion Committee, Subcommittee Chair

PUBLIC SERVICE:

1996-	Founder, consultant, Scientific Advisory Board member, Genteric Corporation, Alameda, CA.
1999-	Scientific Advisory Board Member, Cythera Corporation/Novocell Corporation, San Diego, CA.
2004-	Founder , Eilyon LLP, San Francisco, CA.
2005-	Advisory Board member, Nutrihand, Inc., Mountain View, CA.
2005-	Scientific Advisory Board Member, Tethys Bioscience, Inc., Emeryville, CA.

TEACHING and MENTORING

FORMAL SCHEDULED CLASSES FOR UCSF STUDENTS (2003-2006):

Qtr	Academic Yr	Course No & Title	Teaching Contribution	Units	Class
W	1994-2005	BMS225A: Tissue and Organ Biology	Director, lecturer, paper discussion facilitator	3.5	18
S	2005-	BMS225B: Tissue and Organ Biology	Director, lecturer, paper discussion facilitator	3.5	18
S	1999-	Endocrine Fellows Review Course	Lecturer		12
F	2002-2005	Metabolism and Nutrition Block (MS2)	Co-director, lecturer, small group facilitator		140
S	2006-	Metabolism and Nutrition Block (MS1)	Co-director, lecturer, small group facilitator		140

PREDOCTORAL STUDENTS SUPERVISED OR MENTORED (Past 5 years):

Dates	Name	Program or School	Faculty Role	Current Position
2001	Jennifer Wade	UCSF, BMS graduate program	Oral exam committee	PhD student
2002	Heiko Loehr	Univ. of Darmstadt, Germany, undergrad	Supervised research semester	PhD student
2002	Beverly See	Brown University, undergraduate	Supervised summer research	Medical student
2002	Suchitra Ananthnarayan	UCSF, BMS graduate program	Supervised research rotation	PhD student
2002	Michael Verzi	UCSF, BMS graduate program	Oral exam committee	PhD student
2003	Michelle Shih	UCSF, BMS graduate program	Oral exam committee	PhD student
2003	Claudio Villanueva	UCSF, BMS graduate program	Oral exam committee, chair	PhD student
2003	Janet Lau	UCSF, BMS graduate program	Oral exam committee	PhD student
2003, 2005	Won-Suk Chung	UCSF, BMS graduate program	Supervised research rotation Oral exam committee, chair	PhD student
2003-	Janet Lau	UCSF, BMS graduate program	Oral exam committee Thesis committee, chair	PhD student
2004	Nicole Neubauer	Univ. of Copenhagen graduate program	Supervised research semester	PhD student
2004,	Jenny Zhang	High school student	Supervised summer	Undergraduate,

2005			research	Stanford University
2004	Mai-king Chan	Harvard University, undergraduate	Supervised summer research	Undergraduate, Harvard University
2004-	Patrick Heiser	UCSF, BMS graduate program	Thesis committee	PhD student
2005	Gilberto Palacios	UCSF medical student	Supervised summer research	Medical student
2005	Aaron Bunnell	UCSF medical student	Supervised summer research	Medical student
2005	Cory Nicholas	UCSF, BMS graduate program	Oral exam committee, chair	PhD student

POSTDOCTORAL FELLOWS SUPERVISED OR MENTORED:

Dates	**Fellow**	**Institution where Degree Received**	**Title of Project in German Lab**	**Present Position or Source of funding**
1993-1995	Hiroki Odagiri, MD, PhD	Hirosaki Univ, Japan	Metabolic regulation of insulin gene expression.	Asst Prof, Department of Surgery, Hirosaki Univ, Japan
1994-1996	Andrea Hayes-Jordan, MD	Dartmouth Med School	Development of the ß-cell glucose sensor.	Assistant Professor, Georgetown University Medical School, Washington, DC
1994-1999	Maike Sander, MD	Frei Univ of Berlin Med School	Transcription factors involved in beta-cell differentiation.	Assistant Professor, UC Irvine
1994-2000	Steve Griffen, MD	Med College of Wisconsin	Metabolic regulation of insulin gene transcription.	Assistant Prof, Endocrinology, Clinical Nutrition/Vascular Biology, UC Davis
1995-1997	Jeffrey Johnson, PhD	Univ of Texas	Protein-protein interactions in insulin gene transcription	Director, Islet Biology, Metabolex, Inc., Hayward, CA
1996-1998	Hooi Ee, MD, PhD	Univ of Western Australia	Role of the Pax genes in insulin gene transcription.	Asst Prof, Dept Gastroenterolog Sir Charles Gairdner Hospital, Perth, Australia
1996-1998	Ohneda, Kinuko, PhD	Tohoku Univ, Japan	Protein-protein interactions in insulin gene transcription	Research Fellow, Univ of Tsukuba, Japan
1996-2002	Maria Wilson, PhD	Univ of Aberdeen, Scotland	Role of Lmx1.1 in ß-cell differentiation.	Senior Scientist, Metabolex, Inc., Hayward, CA
1997-1998	David Olson, PhD	Princeton Univ	Insulin gene therapy.	Project Leader, Genteric Corporation, Alameda, CA
1997-1999	Valerie Schwitzgebel, MD	Univ of Fribourg & Berne, Switzerland	Role of bHLH proteins in ß-cell differentiation.	Asst Prof, Dept of Ped Endocrin & Diabetes, Univ of Geneva, Switzerland
1997-2000	Hirotaka Watada, MD, PhD	Osaka Univ, Japan	Regulation of transcription factor expression in ß-cells.	Asst Prof, Dept Med, Metab & Endocrinol, Juntendo Univ School of Med, Hongo, Japan
1997-	Stuart Smith, PhD	Univ of Aberdeen, Scotland	Role of Pax4 in ß-cell differentiation.	JDF Senior Postdoc Fellowship
1998-2000	Raghu Mirmira, MD,PhD	Univ of Chicago	Role of Nkx6.1 in ß-cell gene expression.	Assoc Prof, Dept Medicine, Univ of Virginia, Charlottesville, VA

1999-2000	Jane Lee, MD	UC Los Angeles	Role of neurogenin3 in islet development	Assistant Prof, Department of Pediatrics, UCSF
1999-2002	Caroline Mrejen, PhD	Univ of Paris VII France	Role of Nkx2.2 in ß-cell differentiation	Adj Asst Prof, Dept of Growth and Development, UCSF
2000-2004	Rosa Gasa, PhD	Univ of Barcelona, Spain	Role of Nkx6.1 in ß-cell differentiation	Researcher Ramon y Cajal, Lab Exp Diabetes, IDIBAPS, U of Barcelona
2001-	Yasuhiro Kosaka, PhD	Hiroshima Univ, Japan	Identification of pancreatic stem cells	ADA Postdoc Fellowship
2001-2004	Yoshinori Shimajiri, MD,PhD	Okinawa University, Japan	Factors controlling beta-cell determination	Fellow, Dept of Medicine Wakayama University, Japan
2002-	Anna Kalousova, PhD	Charles Univ, Czech Republic	Role of bHLH factors in islet cell differentiation	Larry L. Hillblom Foundation
2003-	Francis Lynn, PhD	Univ of British Columbia	Role miRNA in ß-cell differentiation	JDRF Postdoc Fellowship
2003-	Nada Nekrep, PhD	University of Ljubljana, Slovenia	Identification of multipotent stem cells in the pancreas	American Diabetes Association
2003-	Yasuharu Ota, MD, PhD	Yamaguchi Univ., Japan	Role of Pet1 in ß-cell differentiation	American Diabetes Association
2005-	Bruce Adams, PhD	University of Victoria	Pancreatic transcription factors in zebrafish and mice	JDRF Postdoc Fellowship
2005-	Anastasia Mavropoulos, PhD	University of Liege (Belgium)	Role miRNA in ß-cell differentiation	Larry L. Hillblom Foundation

INFORMAL TEACHING:

1987- Discussant, Endo. and Metab. Clinical Conference. Weekly.
1989- Attending physician, Diabetes Clinic. 1/2-day clinic 2X/month. 3-6 students/residents/fellows.
1993- Lecturer, discussant and faculty coach, Biomedical Sciences Journal Club. Weekly.
1994- Attending rounds, Endocrinology and Metabolism Consult Service. 6 weeks per year.
2002- Reviewer at the Poster Session at Career & Research Days. Yearly.
2004- Presenter at the School of Medicine Career Fair. Discuss careers in Endocrinology. Yearly.

FACULTY MENTORING (Past 2 years):

Dates	**Name**	**Position while Mentored**	**Mentoring Role**	**Current Position**
1999-05	Christian Vaise, MD	Assistant Professor	Academic and Research Collaborator/Advisor	Assoc. Prof. in Res., Medicine, UCSF
1999-05	Matthias Hebrok, PhD	Assistant Professor	Academic and Research Collaborator/Advisor	Assoc. Prof. in Res., Medicine, UCSF
2003-	Mark Anderson, MD, PhD	Assistant Professor	Scientific, Grant, and Career Advisor	Asst. Prof. in Res., Medicine, UCSF
2004-	Michael McManus, PhD	Assistant Professor	Research Collaborator/ Formal Mentor	Asst. Prof. in Res., Micro&Immuno, UCSF

2004	Eric Nakakura, MD, PhD	Assistant Professor	Scientific and Grant Advice	Asst. Prof. in Res., Surgery, UCSF
2005	Paolo Rinaudo, MD, PhD	Assistant Professor	Scientific and Grant Advice	Asst. Prof. in Res., ObGyn, UCSF

TEACHING AIDS:

Five syllabus chapters (Diseases of the HPA Axis, Introduction to Diabetes and Type 1 Diabetes, Energy Metabolism and Obesity, Type 2 Diabetes, Genetics of Obesity and Type 2 Diabetes) for the Metabolism and Nutrition Block, used by all UCSF Medical Students. Updated yearly.

TEACHING AWARDS AND NOMINATIONS:

Nominated for Outstanding Lecture, Med I Teaching Awards, 1994 & 1995.
Nominated for Excellence in Small Group Instruction, Med I Teaching Awards, 1998.
Nominated for Essential Core Teaching Award, 2005.

SUMMARY OF TEACHING HOURS:

2003-04
511 total hours of teaching (including preparation).
Formal class or course teaching hours: 91
Informal teaching hours: 400
Mentoring hours: 20

2004-05
527 total hours of teaching (including preparation).
Formal class or course teaching hours: 97
Informal teaching hours: 410
Mentoring hours: 20

2005-06
592 total hours of teaching (including preparation).
Formal class or course teaching hours: 162 (Metabolism and Nutrition Block will move to the first year and thus be run twice).
Informal teaching hours: 410
Mentoring hours: 20

RESEARCH AND CREATIVE ACTIVITIES

RESEARCH AWARDS AND GRANTS

CURRENT:

Source:	NIH/NIDDK, 1R01 DK21344-24
Title:	Differentiation in the Endocrine and Exocrine Pancreas
Role:	P.I.
Effort:	20%
Inclusive Fund Dates:	4/1/04-3/31/08
Total Award:	$880,00 (direct costs)
Yearly Award:	$220,000 (direct costs)

Source:	NIH/NIDDK 1 U19 DK61245
Title:	Mol. Control of Panc. Islet Development (Beta-Cell Biol. Consortium)
Role:	P.I./Project Leader
Effort:	15%
Inclusive Fund Dates:	9/30/01-9/29/05
Total Award:	$4,246,575 (direct costs, Total)/ $800,000 (direct costs, Project)
Yearly Award:	$1,058, 072 (direct costs, Total)/ $200,000 (direct costs, Project)

Source:	NIH/NIDDK 5P30 DK063720
Title:	Diabetes and Endocrinology Research Center (DERC)
Role:	P.I.
Effort:	5%
Inclusive Fund Dates:	5/1/03-1/31/08
Total Award:	$4,000,000 (direct costs, entire Center)
Yearly Award:	$800,000 (direct costs, entire Center)

Source:	Nora Eccles Treadwell Foundation
Title:	The Role of bHLH Proteins in Beta-Cell Development
Role:	P.I.
Effort:	5%
Inclusive Fund Dates:	8/1/98-7/31/08
Total Award:	$1,250,000 (direct costs)
Yearly Award:	$125,000 (direct costs)

Source:	American Diabetes Association
Title:	Mentor-Based Postdoctoral Fellowship
Role:	P.I.
Effort:	N.A.
Inclusive Fund Dates:	7/1/03-6/30/07
Total Award:	$180,000 (direct costs)

Yearly Award:	$45,000 (direct costs)
Source:	Larry L. Hillblom Foundation
Title:	Islet Genesis Network
Role:	P.I.
Effort:	20%
Inclusive Fund Dates:	9/1/02-8/30/06
Total Award:	$1,900,000 (direct costs)
Yearly Award:	$450,000 (direct costs)
Source:	American Diabetes Association
Title:	Engineering Islet Cell Development
Role:	P.I.
Effort:	20%
Inclusive Fund Dates:	1/1/04-12/31/07
Total Award:	$1,000,000 (direct costs)
Yearly Award:	$250,000 (direct costs)

PENDING:

Source:	NIH 1 U19 DK61245
Title:	Mol. Control of Panc. Islet Development (b-Cell Biol. Consortium)
Role:	P.I./Project Leader
Effort:	15%
Inclusive Fund Dates:	9/30/05-9/29/10
Total Award:	$4,246,575 (direct costs, Total)/ $800,000 (direct costs, Project)
Yearly Award:	$1,058, 072 (direct costs, Total)/ $200,000 (direct costs, Project)

PEER REVIEWED PUBLICATIONS:

PRIMARY RESEARCH PUBLICATIONS:

1. German, M. and Syvanen, M. Incompatibility between bacteriophage lambda and the sex factor F. *Plasmid* 8:207-210 (1982).
2. German, M., Moss, L.G. and Rutter, W.J. Regulation of insulin gene expression by glucose and calcium in primary islet cultures. *J. Biol. Chem.* 265:22063-22066 (1990).
3. German, M., Blanar, M., Nelson, C., Moss, L.G., and Rutter, W. Two related helix-loop-helix proteins participate in separate cell-specific complexes that bind the insulin enhancer. *Molecular Endocrinology* 5:292-299 (1991).
4. German, M., Moss, L.G., Wang, J., Rutter, W.J. The insulin and islet amyloid polypeptide genes contain similar cell-specific promoter elements that bind identical b-cell nuclear complexes. *Mol. Cell. Biol.* 12:1777-1788 (1992).

5. German, M., Wang, J., Chadwick, R., Rutter, W. J. Synergistic activation of the insulin gene by a LIM-homeodomain protein and a basic helix-loop-helix protein: building a functional insulin minienhancer complex: *Genes & Dev.* 6:2165-2176 (1992).
6. German, M. Glucose sensing in pancreatic islet b-cells: the key role of glucokinase and the glycolytic intermediates. *Proc. Natl. Acad. Sci. USA* 90:1781-1785 (1993).
7. German, M. and Wang, J. The insulin gene contains multiple transcriptional elements that respond to glucose. *Mol. Cell. Biol.* 14:4067-4075 (1994).
8. Rudnick, A., Ling, T., Odagiri, H., Rutter, W., German, M. Pancreatic islet ß-cells express a diverse set of homeobox genes. *Proc. Natl. Acad. Sci. USA* 91: 12203-12207 (1994).
9. German, M., Wang, J., Fernald, A., Espinosa, R., Le Beau, M., Bell, G. Localization of the genes encoding two transcription factors, lmx-1 and cdx-3, regulating insulin gene expression to human chromosomes 1 and 13. *Genomics* 24: 403-404 (1994).
10. Kennedy, G., German, M., Rutter, W. The minisatellite in the diabetes susceptibility locus IDDM2 regulates insulin transcription. *Nature Genetics* 9: 293-298 (1995).
11. Tsaur, M.-L., Menzel, S., Lai, F.-P., Espinosa, R., Concannon, P., Spielman, R., Hanis, C., Cox, N., LeBeau, M., German, M., Jan, L., Bell, G., Stoffel, M. Isolation of a cDNA clone encoding a KATP-channel-like protein expressed in insulin secreting cells, localization of the human gene to chromosome band 21q22.1, and linkage studies with NIDDM. *Diabetes* 44:592-596 (1995).
12. Stoffel, M., Tokuyama, Y., Trabb, J., German, M., Tsaur, M.-L., Jan, L., Polonsky, K., and Bell, G. Characterization of a rat ATP-regulated potassium channel-like protein, KATP2: sequence, tissue distribution, and decreased expression in pancreatic islets of diabetic animals. *Biophys. Biochem. Res. Com.* 212:894-899 (1995).
13. Odagiri, H., Wang, J., German, M. Function of the human insulin promoter in primary islet cultures. *J. Biol Chem.* 271:1909-1915 (1996).
14. Collins, A., German, M., Jan, N., Jan, L., Zhao, B. A strongly inwardly rectifying K+ channel that is sensitive to ATP inhibition. *J. Neurosci.* 16:1-9 (1996).
15. Inoue, H., German, M., Veile, R., Rudnick, A., Helms, C., Donis-Keller, H., Permutt, M. A. Isolation, characterization, and chromosomal mapping of the human Nkx6.1 gene, a new pancreatic islet homeobox gene. *Genomics* 40:367-370 (1997).
16. Wang, J., Shen, L., Najafi, H., Kolberg, J., Matschinsky, F., Urdea, M., German, M. Regulation of insulin preRNA splicing by glucose. *Proc. Nat. Acad. Sci. USA* 94:4360-4365 (1997).
17. Iannotti, C., Inoue, H., Bernal, E., Aoki, M., Yukio, T., Liu, L., Donis-Keller, H., German, M., Permutt, M. A. Identification of a human LMX1 (LMX1.1)-related gene, LMX1.2: tissue-specific expression and linkage mapping on chromosome 9. *Genomics* 46:520-524 (1997).
18. Johnson, J., Zhang, W., Rutter, W.J., German, M. Transcriptional synergy between LIM-homeodomain proteins and basic helix-loop-helix proteins: the LIM2 domain determines specificity. *Mol. Cell. Biol.* 17:3488-3496 (1997).
19. Sander, M., Neubuser, A., Kalamaras, J., Ee, H. C., Martin, G. R., German, M. Genetic analysis reveals that PAX6 is required for normal transcription of pancreatic hormone genes and islet development. *Genes & Development* 11:1662-1673 (1997).
20. Goldfine, I. D., German, M., Tseng, H., Bolaffi, J., Chen, J.-W., Olson, D., Rothman, S. The endocrine secretion of human growth hormone and insulin by exocrine glands of the gastrointestinal tract. *Nature Biotech.* 15:1378-1386 (1997).

21. Sussel, L., Kalamaras, J., Hartigan-O'Connor, D. J., Meneses, J., Pedersen, R., Rubenstein, J., German, M. Mice lacking Nkx2.2 have diabetes due to an arrest in pancreatic ß-cell differentiation *Development* 125: 2213-2221(1998).

22. Furuta, H., Hirokawa, Y., Iwasaki, N., Hara, M., Le Beau, M., Davis, E., Ogata, M., Iwamoto, Y., German, M., Bell, M. ß-cell transcription factors and diabetes mellitus: mutations in the coding region of the BETA2/NeuroD (NEUROD1) and Nkx2.2 (NKX2B) genes are not associated with MODY in Japanese *Diabetes* 47: 1356-1358 (1998).

23. Sander, M., Griffen, S., Wang, J., German, M. A novel glucose responsive element in the human insulin gene promoter functions uniquely in primary cultured islets *Proc. Nat. Acad. Sci. USA* 95: 11572-11577 (1998).

24. Cabrera-Valladares, G., German, M., Matschinsky, F., Wang, J., Fernandez-Mejia, C. Effect of retinoic acid on glucokinase activity and gene expression in primary cultures of pancreatic islets *Endocrinology* 140:3091-3096 (1999).

25. Smith, S., Ee, H., Conners, C., German, M. Paired-homeodomain transcription factor PAX4 acts as a transcriptional repressor in early pancreatic development *Mol. Cell. Biol.* 19:8272-8280 (1999).

26. Romero-Navarro, G., Cabrera-Valladares, G., German, M., Matschinsky, F, Velazquez, A., Wang, J., Fernandez-Mejia, C. Biotin regulation of pancreatic glucokinase and insulin in primary cultured rat islets and in biotin deficient rats *Endocrinology* 140:4595-600 (1999).

27. Ohneda, K., Mirmira, R., Wang, J., Johnson, J., German, M. The homeodomain of PDX-1 mediates multiple protein-protein interactions in the formation of a transcriptional activation complex on the insulin gene promoter *Mol. Cell. Biol.* 20:900-911 (2000).

28. Dreyer, S., Morello, R., German, M., Zabel, B., Winterpacht, A., Lundstrom, G., Horton, W., Oberg, K., Lee, B. LMX1B transactivation and expression in nail patella syndrome. *Human Mol. Gen.* 2000: 1067-1074 (2000).

29. Mirmira, R., Watada, H., German, M. Beta-cell differentiation factor Nkx6.1 contains distinct DNA-binding interference and transcriptional repression domains *J. Biol. Chem.* 275:14743-14751 (2000).

30. Schwitzgebel, V., Scheel, D., Conners, J., Kalamaras, J., Lee, J., Anderson, D., Johnson, J., German, M. Expression of Neurogenin3 reveals an islet cell precursor population in the pancreas *Development* 127:3533-3542 (2000).

31. Watada, H., Mirmira, R., Kalamaras, J., German, M. Intramolecular control of transcriptional activity by the NK2 specific domain in NK-2 homeodomain proteins *PNAS USA* 97:9443-9448 (2000).

32. Sander, M., Paydarl, S., Ericson, J., Briscoe, J., Berber, E., German, M., Jessell, T., Rubenstein, J. Ventral neural patterning by Nkx homeobox genes: Nkx6.1 controls somatic motor neuron and ventral interneuron fates *Genes & Development,* 14:2134–2139 (2000).

33. Watada, H. , Mirmira, R., Leung, J., German, M. Transcriptional and translational regulation of b-cell differentiation factor Nkx6.1 *J. Biol. Chem.* 275: 34224-34230 (2000).

34. Horikawa, Y., Horikawa, Y., Cox, N., Iwasaki, N., Ogata, M., Iwamoto, Y., Schwitzgebel, V., German, M., Bell, G. Beta-cell transcription factors and diabetes: no evidence for diabetes-associated mutations in the coding region of the basic-helix-loop-helix transcription factor neurogenic differentiation 4 (*NEUROD4*) in Japanese patients with MODY. *Diabetes* 49:1955-1958 (2000).

35. Smith, S., Watada, H., Scheel, D., Mrejen, C., German, M. Autoregulation and MODY transcription factors control the human *PAX4* promoter. *J. Biol. Chem.* 275: 36910-36919 (2000).

36. Sander, M., Sussel, L., Conner, J., Schwitzgebel, V., Hayes-Jordan, A., German, M. Homeobox gene Nkx6.1 lies downstream of Nkx2.2 in the major pathway of beta-cell formation in the pancreas *Development* 127: 5533-5540 (2000).

37. Griffen, S., Wang, J., German, M. A genetic defect in beta-cell gene transcription segregates independently from the *Fa* locus in the ZDF rat. *Diabetes* 50:63-68 (2001).

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